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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,676	01/26/2004	Peter Rohnert	13183.0037	9441

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EXAMINER	
SOLOLA, TAOFIQ A	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/764,676	ROHNERT ET AL.	
	Examiner	Art Unit	
	Taofiq A. Solola	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *30 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *45-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *45-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 45-86 are pending in this application.

Claims 1-44 are cancelled.

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.117(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/30/06 has been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 45-63, 67-68, 79-80, are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The structural definitions of "prodrug" of ambroxol in claims 45, 55, 60-61, 67-68, 79-80, is not disclosed in the specification so as to determine the structures of compounds that are included and/or excluded by the term. By deleting the term the rejection would be overcome.

Claims 55-63, 74-81, 83-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for preventing or treating the diseases listed in the claims. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The claimed methods of use are not believable on their face.

"'In the context of determining whether sufficient "utility as a drug, medicant, and the like in human therapy" has been alleged, it is proper for the examiner to ask for substantiating evidence unless one with ordinary skill in the art would accept the [compounds and the utilities] as obviously correct." *In re Jolles*, 628 F.2d 1327, 1332 (Fed. Cir. 1980), citing *In re Novak*, 306 F.2d 924 (CCPA 1962); see 340 F.2d 974, 977-78 (CCPA 1965).

"A specification disclosure which contains a teaching of the manner and process of making and using the invention . . . must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), Id. At 1566, quoting *Marzocchi*, 439 F.2d 220, 223 (CCPA 1971); *Fiers v. Revel,* 984 F.2d 1164, 1171-72 (Fed. Cir. 1993), quoting *Marzocchi*, 439 F.2d at 223; see also *Armbruster*, 512 F.2d 676, 677 (CCPA 1975); *Knowlton*, 500 F.2d 566, 571 (CCPA 1974); *Bowen*, 492 F.2d 859 (CCPA 1974); *Hawkins*, 486 F.2d 569, 576 (CCPA 1973).

Where there is "no indication that one skilled in the art would accept without question [the instant compounds and method of use] and no evidence has been presented to demonstrate that the claimed products do have those effects *Novak*, 306 F.2d at 928, an applicant has failed to sufficiently demonstrate sufficient utility and therefore cannot establish enablement."' *In re Rasmusson,* 75 USPQ2d 1297 (CAFC 2005). The claimed utilities are not enabled without undue experimentation for the following reasons:

For rejection under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988):

1) Breadth of claims, 2) Nature of invention, 3) State of prior art, 4) Level of ordinary skill in the art, 5) Level of predictability in the art, 6) Amount of direction and guidance provided by the inventor, 7) Existence of working examples, 8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breath of the claimed invention involves medicinal chemistry. The nature of the invention is in the field of using the instant compositions for treating many disorders due to GSH deficiency. The state of the prior art is what prior art knows about the nature of the invention. There is no known prior art claiming treatment of the various disorders arising from GSH deficiency. The level of ordinary skill in the art is high but only in using the constituents of the compositions for correcting GSH deficiency. For example, see prior arts cited under 35 USC 103(a), *below.* The predictability or lack thereof in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. The lower the predictability, the higher the direction and guidance that must be provided by applicant. In the instant invention the predictability is very low and consequently, the need for higher levels of direction and guidance by applicant. However, the amount of direction and guidance provided by applicant is limited to assays comparing the effects of using the individual compounds with using them in combination. There are a very large variety of sources for the listed disorders because different mechanisms are involved. It is well known in the art that the mechanism of a specific disorder would dictate the choice of how to treat it. Additionally, there is no evidence in the specification that established correlation between applicant's experiments and all the possible mechanisms giving rise to the various disorders. See Ex parte Mass, 9 USPQ2d 1746, 1987. Therefore, the quantity of experimentation required to use the compound as claimed, based on applicant's limited disclosure would be undue burden because, one of ordinary skill in the art would have to perform significant amount of experiments.

MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding any of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. The purpose of 35 USC 112 is to obviate the need for this type of experimentation. *In re Borkowski,* 164 USPQ 642 (CCPA,1970). See also, *Univ. of Rochester v. G.D.Searle & Co,* 68 USPQ2d 1424 (DC WNY, 2003).

There is no conclusive evidence in the specification that the compositions alone would treat all the diseases listed in the claims. At the very best the compositions may be useful as supplement. Appropriate correction is required. There is no evidence in the specification that applicant is the first to discover using ambroxol, inhibitor of ACE or α-lipoic acid to improve GSH level in the body and treating or preventing diseases arising therefrom.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 45-68, 74-81, 83-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

For reasons set forth above under 35 USC 112, first paragraph, claims 45-63, 67-68, 74-81, 83-86 are indefinite. See the Examiner's suggestions above.

Claims 67-68 are broader than the scope of claim 64, and claims 79-80 are broader than the scope of claim 74. The term "prodrug" in claims 67-68; and claims 79-80, lacks proper

antecedent basis in claims 64 and 74 respectively. By deleting the term the rejection would be overcome.

Claim 47 is a duplicate of 46. The term "composition" implies pharmaceutical carriers, additives and/or adjuvants are inherent in claim 46. Otherwise, claim 46 would be a compound. For the same reason claim 59 is a duplicate of 55, 66 duplicate of 64, 78 duplicate of 74, and claim 86 is a duplicate of 82. By deleting one of each duplicate the rejection would be overcome.

Claim 86 is confusing and therefore indefinite. The claim is drawn to a method of use, while claim 82, from which it depends, is drawn to composition. Appropriate correction is required.

Applicant's arguments filed 5/30/06 have been fully considered but they are not persuasive. Applicant referenced the argument filed 10/17/05, wherein applicant contends that "prodrug" is defined in the specification, page 11, lines 16-24. Applicant also attached Exhibit A for general description of prodrugs. This is not persuasive because the issue is not generic definition of prodrug but specific structural definition of the prodrugs of ambroxol. In response to enablement rejection, applicant argues that based on the showing of synergistic effect in the specification, one skilled in the art would understand how to treat neurodegenerative diseases. Citing MPEP 716.02(a) and *Merck & Co. Inc. v. Biocraft Lab. Inc.,* 874 F.2d 804, 10 USPQ2d 1843 (CAFC, 1989), applicant contends synergistic effect is enough for unobviousness. This is not persuasive because MPEP 716.02(a) further states: "[h]owever, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected." In the instant case, such additive effect is expected. *Merck & Co.* further states that unobviousness is not overcome where the result is

"[r]eached by means of routine procedures." Applicant's assay is routine and does not rise to the level of invention under the US patent practice.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 45-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillissen et al., Respiratory Med. (1998), Vol. 92, pages 609-623; further in view of Derick et al., Biochem. Biophy. Research Comm. (1995), Vol. 207(1), pages 258-264 ; Elena et al., Am. J. Physiol. Regulatory Integrative Comp. Physiol., (2000), Vol. 278, pages R572-R577; Sian et al., Annals of Neurology, (1994), Vol. 36(3), pg. 348-355; and Kozhevnikova et al., Bull. Experimental Biol. and Med. (1999), Vol. 128(11), pg. 535-537.

Applicant claims a composition comprising ambroxile and Angiotesin-converting enzyme inhibitor (ACE inhibitor) optionally, α-lipoic acid and method of use for treating neurodegenerative diseases. In preferred embodiment applicant claims several dosages, types of composition, and routes of administration.

Determination of the scope and content of the prior art (MPEP §2141.01

Gillissen et al., teach a composition comprising ambroxile as anti-oxidant therapy (correcting GSH deficiency). Derick et al., teach a composition comprising α-lipoic acid for increasing intracellular GSH. Elena et al., teach a composition comprising enalapril or captopril for enhancing GSH-dependent anti-oxidant defenses (correcting a disturbance of thiol-disulfide status or GSH deficiency). Sian et al., teach reduced level of GSH in patents suffering

Parkinson's disease and neurodegenerative disorders. Kozhevnikova et al., teach the beneficial effect of ACE inhibitors in cerebral ischemia.

Ascertainment of the difference between the prior art and the claims (MPEP ∋2141.02)

The difference between the instant invention and that of Gillissen et al., and Derick et al., is that applicant claims a composition comprising one or more of ambroxile, ACE inhibitor(s) and α-lipoic acid instead of a composition comprising ambroxile by Gillissen et al., and a composition comprising α-lipoic acid by Derick et al., and a composition comprising enalapril or captopril by Elena et al. Applicant also claims several dosages, types of composition, routes of administration and treatment of disorders arising from GSH deficiency.

Finding of prima facie obviousness--rational and motivation (MPEP ∋2142.2413)

The combination of compounds for a certain function where the compounds are known to perform the function individually is prima facie obvious. "The idea of combining them flows logically from their having been individually taught in the prior art[s]. Applicant's claim require no more than mixing together the compositions." *In re Kerkhoven,* 205 USPQ 1069 (1980). See also, *In re Susi,* 169 USPQ 423, 426 (CCPA, 197). "Assuming that [ambroxile, α-lipoic acid and ACE inhibitors] together produce an effect somewhat greater than sum of their separate effects . . . claim to their joint use is not patentable." *In re Crockett,* 126 USPQ 186 (CCPA, 1960). Therefore, the instant invention is prima facie obvious from the teachings of Gillissen et al., Derick et al., Elena et al., Sian et al., and Kozhevnikova et al. Claiming dosages, types of composition, routes of administration and treatment of disorders arising from GSH deficiency is not patentable significant because they do not rise to the level of invention under US patent practice.

Knowing that ambroxile, α-lipoic acid and ACE inhibitors, individually, are useful for Parkinson's disease , neurodegenerative disorders and cerebral ischemia, one of ordinary skill

in the art would have known to use them individually or combine them in a composition for the diseases. The motivation to combine them is from the teachings of Gillissen et al., Derick et al., and Elena et al., that ambroxile, α-lipoic acid, and enalapril or captopril, respectively are useful for correcting GSH deficiency. It is also from the teachings of Sian et al., and Kozhevnikova et al., and from the common practice in medicine of using cocktail medication.

Applicant should note that correcting GSH deficiency with a compound and treating diseases arising from GSH deficiency with the compound is an obvious selection available to the preference of one of ordinary skill in the art, and are not patentable distinct under US patent practice.

Applicant's arguments filed 5/30/06 have been fully considered but they are not persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant asserts that Gillissen et al., do not teach correcting GSH deficiency. This is not persuasive because applicant fails to support the assertion with a conclusive evidence. Citing MPEP 716.02(a) and *Merck & Co. Inc. v. Biocraft Lab. Inc.,* 874 F.2d 804, 10 USPQ2d 1843 (CAFC, 1989), applicant contends synergistic effect is enough for unobviousness. This is not persuasive because MPEP 716.02(a) further states: "however, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected." In the instant case, such additive effect is expected. *Merck & Co.* further states that unobviousness is not overcome where the result is "[r]eached by means of routine procedures." Applicant's assay is routine and does not rise to the level of invention under the US patent practice.

Abstract

The abstract is still too long. Appropriate correction is required.

Drawing

The drawing submitted on 1/26/04 is objected to because hand written inscriptions on each page.

Telephone Inquiry

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Taofiq A. Solola, PhD. JD., whose telephone number is (571) 272-0709.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Joseph McKane, can be reached on (571) 272-0699. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

TAOFIQ SOLOLA
PRIMARY EXAMINER
Group 1626

July 1, 2006